**Remarks/Arguments:**

Claims 70-78 are pending in this application.

As indicated above, claim 70 is amended hereby to correct apparent errors in the Examiner's Amendment attached to the Notice of Allowability. Specifically, the instant amendment reinstates "within the target nucleic acid sequence" in each of steps "c)" and "d)." The language reinstated, hereby (i.e., the language being found in claim 70 prior to the Examiner's Amendment), appears to have been inadvertently deleted by the Examiner's Amendment, since the reinstated language is necessary to properly define Applicant's claimed invention; and, moreover, since the Examiner's Amendment was not authorized by Applicant's representative, statements accompanying the Examiner's Amendment to the contrary, notwithstanding.

According to comments accompanying the Examiner's Amendment: "Authorization for this Examiner's Amendment was given in a telephone interview with William Player on or about 5-10-04" (Notice of Allowability, page 2). The aforesaid statement appears to reflect a misunderstanding, since Applicant's undersigned representative did not authorize the Examiner's Amendment – neither in a telephone interview on or about May 10, 2004, nor at any other time.

An Examiner's Amendment had been discussed, and Applicant's undersigned representative did agree to consider the proposed draft of an Examiner's Amendment sent by facsimile; a copy of the facsimile transmission of the proposed Examiner's Amendment, with the word "Draft" handwritten by the Examiner on pages 1 and 2, thereof (transmitted May 10, 2004). The Notice of

Allowability, containing the Examiner's Amendment, was received without Applicant's undersigned representative having responded to the proposed draft of the Examiner's Amendment.

***Comments on Statement of Reasons for Allowance***

Applicant finds the Examiner's Reasons for Allowance (Notice of Allowability, page 4) somewhat difficult to understand; specifically, the last sentence of the first full paragraph:

> The instant invention is free of the prior art of Stull, James and Probst because the instant invention teaches a method to facilitating optimal selection of antisense oligonucleotide targets by using thermodynamic indices to calculate the free energy of secondary structure (Sscore), while taking into consideration the local mRNA secondary structures at the target site, and free energy estimations of the duplex score (Dscore) and determining the differences between the Dscore and the Sscore (e.g., Cscore).

As set forth in the Response filed September 11, 2003 (pages 4-5):

> Stull (newly cited) teaches a method to facilitate the optimal selection of antisense oligonucleotide targets. The method relies on the use of three thermodynamic indices to calculate the free energy ($\Delta G$) of secondary structure formation and not to calculate G-contents. These indices include a secondary structure score (Sscore) to estimate the strength of local mRNA secondary structures at the antisense oligonucleotide-target site, a duplex score (Dscore) to estimate the ($\Delta G$) formation (free energy) for the antisense to mRNA target suplex, and a competition score (Cscore), which is the difference between the Dscore and the Sscore. Thus, the $\Delta G$ calculated does not tell anything about the G-content; rather, it indicates the free energy of a duplex, either within the mRNA or between the mRNA and an antisense oligonucleotide. As such, from Stull one skilled in the art could not have deduced a method for the preparation of effective antisense oligonucleotides having the parameters as presently claimed (claim 70). Stull does not teach or suggest that an antisense oligonucleotide should include the features a) to e) recited in present claim 70.70.
>
> Further, Stull does not teach or suggest that consecutive guanosines should be avoided. On the contrary, there are a couple of oligonucleotides efficient in (according to Stull) inhibiting the expression of a target sequence comprising even five consecutive guanosines (see oligonucleotides ss6 in Stull Table 1), four

consecutive guanosines (see oligonucleotide F and M in Stull Table 3), or two series of three consecutive guanosines (see ISIS1574 in Stull Table 4).

Additionally, the oligonucleotide "G" in Stull Table 3 does not comply with the ratio

[3H-bond-R]/[3H-bonds-R + 2H-bonds-R],

which should lie between 0.33 and 0.86, since the ratio of the given oligonucleotide is 0.93. Therefore, Stull effectively teaches away from the presently claimed invention.

Accordingly, it would not have been obvious (1) that consecutive guanosines in oligonucleotides should be avoided or (2) that the ratio

[3H-bond-R]/[3H-bonds-R + 2H-bonds-R],

should lie between 0.33 and 0.86.

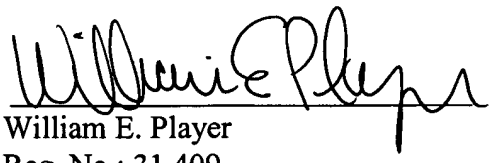
Therefore, Stull effectively teaches away from the presently claimed invention.

Accordingly, Applicant submits that the thermodynamic indices of Stull disclose nothing about the features of the invention as provided, broadly, in present claim 70.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By: 
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